Chromosome aberration study of tetrahydroisoquinoline compounds, THI52 and THI53 as a drug candidate of the cardiovascular system

Kim YJ[o1], Park HJ[1], Yun HS[2], Chang KC[3], Lee DH[4], Ryu JC[1]

[1]Toxicology Laboratory, Korea Institute of Science and Technology,Seoul,136-650,Korea, [2]NPRI, Seoul National University, [3]Gyeongsang National Univ. College of Medicine and [4]Dept. Chemistry, Sogang Univ.

To clarify the toxicity of tetrahydroisoquinoline compounds THI52 and THI53, as a drug candidate of the cardiovascular system, we performed the chromosome aberration assay with Chinese hamster lung (CHL) cell lines. First of all, we decided the 50% cell growth inhibition concentration (IC_{50}) of THI52 and THI53 to set the dose-range in CHL cells. The IC_{50} of THI52 and THI53 were 24.3 and 22.08 μg/ml in the presence of S-9 metabolic activation system, and 8.27 and 8.72 μg/ml in the absence of S-9 metabolic activation system, respectively. In CHL cells exposed to THI52, no significant increase of chromosome aberration was observed in the absence of (2.07-8.27 μg/ml) S-9 metabolic activation system. However, in the presence of (6.1-24.3 μg/ml) S-9 metabolic activation system, the chromosome aberration was significantly increased. In CHL cells exposed to THI53, no significant increase of chromosome aberration was observed in the absence of (2.18 - 8.72 μg/ml) S-9 metabolic activation system. In presence of (22.08 μg/ml) S-9 metabolic activation system, however, the chromosome aberration was significantly increased. From these results, THI52 and THI53 revealed no chromosome aberration in the absence of S-9 metabolic activation system in CHL cells. But, in the presence of S-9 metabolic activation system the significant increase of chromosome aberration was observed.

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Measurement of CYP1A1, GST mRNA in monkey brain, intestine, liver.

Lee KW°, Oh HY, K Asaoka and SHeen YY

Ewha womans university, Kyoto university

The induction of specific P-450 enzymes is difficult to study in man, but non-human primates may provide useful models for this purpose. Previous investigation have shown that phennobarbital, 3-methylcholanthrene(3MC) and TCDD induce several P-450 enzymes in the liver and several extrahepatic organs of monkey. The aim of this study was to determine whether treatment of monkeys with 3MC and dibutylphthalate(DBP) causes an induction of CYP 1A1 as a phase I drug metabolizing enzyme, and GST mRNA as a phase II drug metabolizing enzyme in brain, intestine and liver of monkey.
Treatment of monkey with 3MC resulted in a induction of CYP 1A1 mRNA in brain(3-fold), intestine (2.5-fold), and liver(6-fold). But treatment with DBP not significantly induced CYP 1A1 mRNA. The basal level and induction of neonetal monkey CYP 1A1 mRNA is low, compared to that of adult monkey. Treatment with both 3MC and DBP induced GST α, μ, π. The induction of GST α, μ and π is 1.5-2.5fold.

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Differential histopathological effect of glycolic acid, TPA and UVB irradiation in guinea pig skin

Kim HJ°, Hong JT, Nam KT, Park KS, Ryu SR, Lee JK, Ahn KS, Kim JH, Cho DH and Lee SH